Water Soluble Cationic Phosphine Ligands Containing *m*-Guanidinium Phenyl Moieties. Syntheses and Applications in Aqueous Heck Type Reactions

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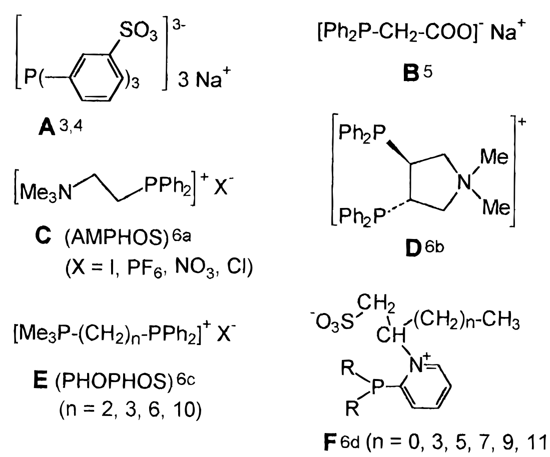
Cationic phosphine ligands containing *m*-guanidinium phenyl substituents $\{Ph_{3-n}P[C_6H_4\text{-}m\text{-}NHC(NH_2)(NMe_2)]_n\}^{n+}\, nCl^-$ ($n = 1-3$) (**17a**−**c**) have been obtained by addition of dimethylcyanamide to the amino groups of tertiary (*m*-aminophenyl)phosphines in acidic medium. The tertiary (*m*-aminophenyl)phosphines $Ph_{3-n}P(C_6H_4\text{-}m\text{-}NH_2)_n$ (**4a**−**c**) were prepared by reaction of (3-[*N,N*-bis(trimethylsilyl)amino]phenyl)magnesium chloride (**1**) with chlorophosphines $Ph_{3-n}PCl_n$ followed by deprotection of the bis(trimethylsilyl)amino groups with methanol. Using a similar protected group synthesis as above, the secondary (*m*-aminophenyl)phosphine $Ph(H)PC_6H_4\text{-}m\text{-}NH_2$ (**7**) could be prepared as well. It may be employed as a building block for the syntheses of chiral bidentate phosphine ligands (**11**, **14**, and **15**) bearing *m*-aminophenyl substituents. The guanidinium phosphines **17b** and **17c** are readily soluble in water. A comparative study of **17b** and **17c**, the aryl alkyl guanidinium phosphines **18** and **19**, and TPPTS ($P(C_6H_4\text{-}m\text{-}SO_3Na)_3$) in the aqueous phase palladium-catalyzed C−C coupling reaction between *p*-iodobenzoate and (trifluoroacetyl)propargylamine shows **17b** to be of surmounting activity.

Introduction

The application of ionic phosphine ligands for the development of catalytically active transition metal reagents in aqueous solvent systems during the last decade is mainly due to the simplification of the catalyst product separation[1,2] and the economy of using water as a solvent in large-scale industrial syntheses. Compared with the widely studied anionic phosphine ligands (e.g., **A** (TPPTS)[3,4] or **B** ($[Ph_2PCH_2COO]^-Na^+$)),[5] the application of cationic phosphines bearing quaternary ammonium (**C** (AMPHOS)[6a] or **D**[6b]), phosphonium (**E** (PHOPHOS)[6c]), or sulfobetaine groups (**F**[6d]) has been investigated but not to a great extent. They were mainly employed as catalysts for the hydrogenation and hydroformylation of olefins. For C−C coupling reactions in aqueous medium, palladium complexes of anionic phosphines are most frequently used as catalysts.[7] Only very few examples of cationic phosphine ligands have been applied.[8]



In a recent publication,[9] we reported on the syntheses and application in aqueous phase Heck type reactions of a novel type of cationic phosphine ligand (e.g., **G**) bearing peripheral guanidinium functions. The introduction of one of the most basic and hydrophilic groups adds pronounced water solubility and anion binding capacity[10] to these ligands. Both features are of significance for their application in transition metal catalyzed transformations of biologically relevant oxo anion substrates such

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(1) Kuntz, E. G. *Chem. Tech.* **1987**, *17*, 570; FR-B 2314190, June 20, 1975, Rhône-Poulenc.
(2) Herrmann, W. A.; Kulpe, J.; Kellner, J.; Riepl, H. DE 3840600 A1, Dec 2, 1988, Hoechst AG. Wiebus, E.; Cornils, B. *Chem. Ing. Techn.* **1994**, *66*, 916.
(3) Herrmann, W. A.; Kulpe, J. A.; Konkol, W.; Bahrmann, H. *J. Organomet. Chem.* **1990**, *389*, 85. Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem.* **1993**, *105*, 1588.
(4)Larpent, C.; Patin, H.; Thilmont, N.; Valdor, J. F. *Synth. Commun.* **1991**, *21*, 495.
(5)Peuckert, M.; Keim, W. *Organometallics* **1983**, *2*, 594.
(6) (a) Smith, R. T.; Ungar, R. K.; Sanderson, L. J.; Baird, M. C. *Organometallics* **1983**, *2*, 1138. Markiewicz, M. K.; Baird, M. C. *Inorg. Chim. Acta* **1986**, *113*, 95. (b) Nagel, U.; Kinzel, E. *Chem. Ber.* **1986,** *119*, 1731. (c) Renaud, E.; Russell, R. B.; Fortier, S.; Brown, S. J.; Baird, M. C. *J. Organomet. Chem.* **1991,** *419*, 403. (d) Fell, B.; Papadogianakis, G. *J. Mol. Catal.* **1991**, *66*, 143.
(7) Bumagin, N. A.; Bykov, V. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Beletskaya, I. P. *J. Organomet. Chem.* **1995**, *486*, 259. Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397. Blart, E.; Genet, J. P.; Safi, M.; Savingnac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505.
(8) Pfeiffer, G.; Chhan, S.; Bendayan, A.; Waegell, B.; Zahra, J. P. *J. Mol. Catal.* **1990**, *59*, 1.
(9) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron* **1995**, *51*, 2325.
(10) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1991; Vol. 2, p 485. Schmidtchen, F. P.; Gleich, A.; Schummer, A. *Pure Appl. Chem.* **1989**, *61*, 1535.

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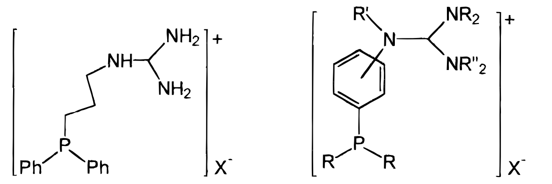
as nucleotides by Heck type or analogous reactions. The guanidinium moiety should exert some directing influence on the reactants by preorientation of the substrates at the periphery of the active catalyst complex.

Low-coordinated Pd(0) complexes of the type PdL_2 (L = phosphine ligands) are generally assumed to be the catalytically active species in C−C cross coupling reactions.[11] Their formation should be favored by the repulsive interaction of the strongly solvated cationic groups if the guanidininium phosphines are considered as ligands. The shielding of the Pd atom will be determined by the rigidity of the spacer unit between the P atoms and the guanidinium moieties, the phenylene bridge (**H**) being more favorable than the flexible trimethylene chain in **G**. Placement of the bulky guanidinium substituent



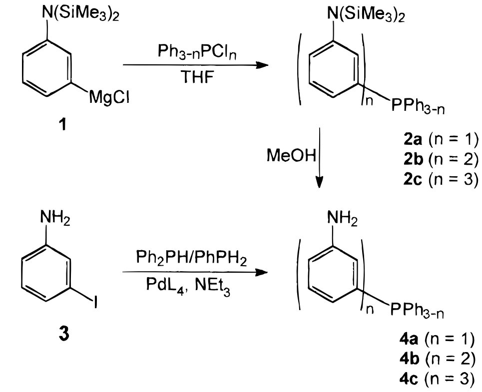
G[9] **H**

in the *ortho*-position should give, however, less stable intermediate Pd(0) complexes and dissociation with precipitation of palladium metal should become a serious side reaction.[12] We concentrated therefore on the *m*-phenylene-bridged guanidinium phosphines (type **H**) bearing the polar group in the same position of the aromatic ring system as in TPPTS. Here, we report on their syntheses based on *m*-aminophenyl-substituted tertiary phosphines and the application of their Pd complexes in aqueous phase Heck type reactions.

Results and Discussion

Syntheses of (*m*-Aminophenyl)phosphines and *m*-Guanidinium Phenylphosphines. For the preparation of the *m*-guanidinium phenylphosphines, a trimethylsilyl-protecting group synthesis[13] was developed in which the guanidinium system was introduced in the last step. Thus, reaction of (3-[*N*,*N*-bis(trimethylsilyl)-amino]phenyl)magnesium chloride (**1**)[13] with Ph_2PCl, $PhPCl_2$, or PCl_3, respectively, gave the silyl derivatives (**2a**−**c**) of the (*m*-aminophenyl)phosphines (Scheme 1). The trimethylsilyl moieties blocked the amino groups to the effects of the P−Cl bonds, since the Si−N bonds were inert to the chlorophosphines under the reaction conditions. The protecting Me_3Si groups in **2a**−**c** could be removed by methanolysis, the (*m*-aminophenyl)phosphines **4a**−**c** being obtained in fair yields. **4a** and **4b** were obtained alternatively in a single-stage synthesis by Pd-catalyzed P−C coupling of diphenyl- or phenylphosphine with *m*-iodoaniline.[14] Compounds **4a**−**c** have been reported in the literature previously.[15a] They were prepared in small quantities by a multistage synthesis

Scheme 1. Syntheses of Tertiary (*m*-Aminophenyl)phosphines



including the reduction of the corresponding (nitrophenyl)phosphines[15b] with molecular hydrogen using Raney nickel as the catalyst. The overall yields were low, and the compounds were only poorly characterized.

The structure of **4c** was established by X-ray structural analysis,[16] showing the molecular dimensions of the skeleton of **4c** to be very close to those reported for triphenylphosphine[17] and *p*-TPPTS.[18]

The technique developed by us for the syntheses of **4a**−**c** can also be used to prepare the secondary (aminophenyl)phosphines (e.g., **7**). Protecting groups for the NH_2 and the PH groups have to be introduced in this case, however. This was achieved by treating dimethyl- or (diethylamino)phenylchlorophosphine[19] with **1** yielding the aminophosphines **5a** and **5b**, respectively. They were, however, not amenable to reduction with $LiAlH_4$ to give the secondary phosphines **8** or **7**. The aminophosphines **5a** or **5b** were therefore transformed by methanolysis into the methoxy derivative **5c**. Its reduction with lithium aluminum hydride gave a mixture of two compounds in a 30:70 ratio. The $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture showed in addition to the signal at $\delta P = -38.8$ ppm of the desired secondary phosphine **8** a resonance at $\delta P = -17.1$ ppm which may be assigned to the diphosphine **9** (cf., δP value for Ph_2PPPh_2 of -14.1 ppm).[20] Reductive cleavage of the P−P bond of **9** with excess sodium and subsequent treatment with ethanol gave **8** in a total yield of ca. 50% (Scheme 2).

If $PhPCl_2$ is treated with an equimolar amount of **1**, the reaction mixture contains the chlorophosphine **6a** ($\delta P = 80.5$ ppm) and the tertiary phosphine **2b** ($\delta P = -6.5$ ppm) in a 1:1 ratio in addition to unreacted $PhPCl_2$ ($\delta P = 160.2$ ppm).[21] The assignment of the signal at $\delta P = 80.5$ ppm to **6a** is based upon the comparison of its δP

(11) Heck, R. F. *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1991; Vol. 27, p 345. Van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323. Calhorda, M. J.; Brown, J. M.; Cooley, N. A. *Organometallics* **1991**, *10*, 1431.

(12) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

(13) Pratt, J. R.; Massey, W. D.; Pinkerton, F. H.; Thames, S. F. *J. Org. Chem.* **1975**, *40*, 1090.

(14) Herd, O.; Hessler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69.

(15) (a) Schiemenz, G. P.; Röhlk, K. *Phosphorus* **1971**, *1*, 187. (b) Schiemenz, G. P.; Röhlk, K. *Chem. Ber.* **1971**, *104*, 1219.

(16) Hessler, A.; Stelzer, O.; Sheldrick, W. S. Unpublished results. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(17) Daly, J. J. *J. Chem. Soc.* **1964**, 3799. Dunne, B. J.; Morris, R. B.; Orpen, A. G. *J. Chem. Soc., Dalton Trans.* **1991**, 653.

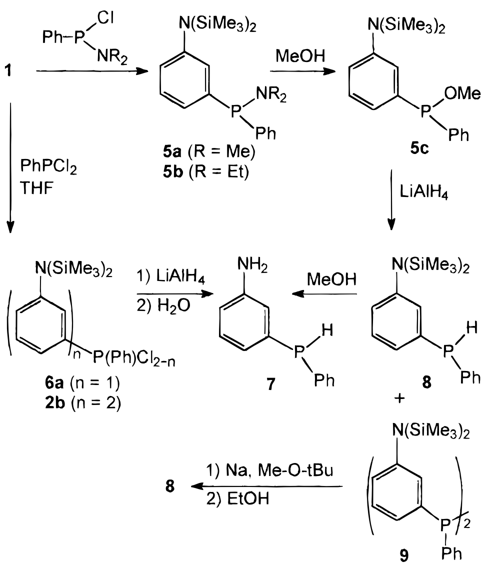
(18) Herd, O.; Hessler, A.; Langhans, K. P.; Stelzer, O.; Sheldrick, W. S.; Weferling, N. *J. Organomet. Chem.* **1994**, *475*, 99.

(19) Frank, A. W. *Organic Phosphorus Compounds* Kosoloapoff, G. M., Maier, L., Eds.; Wiley Interscience: New York, Sydney, Toronto, 1972, Vol. 4, p 402.

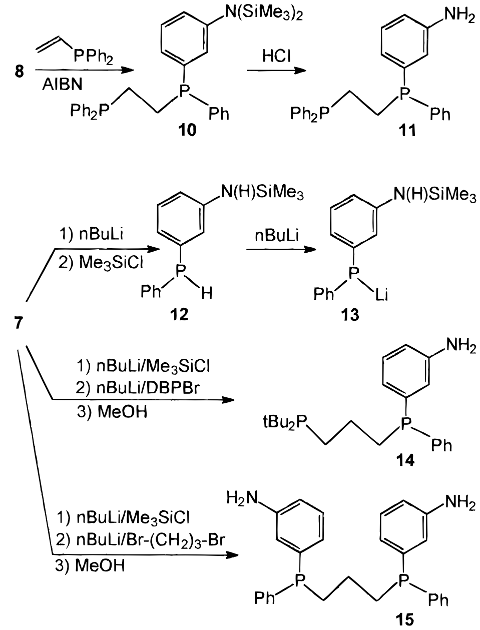
(20) Berger, S.; Braun, S.; Kalinowski, H. O. *NMR Spektroskopie von Nichtmetallen*, *^{31}P-NMR Spektroskopie*; Georg Thieme Verlag: Stuttgart, New York, 1993; Vol. 3.

(21) Fild, M.; Schmutzler, R. *Organic Phosphorus Compounds*; Kosoloapoff, G. M., Maier, L., Eds.; Wiley Interscience: New York, Sydney, Toronto, 1972; Vol. 4, p 75.

Scheme 2. Syntheses of Secondary (*m*-Aminophenyl)phosphines



Scheme 3. Bidentate (*m*-Aminophenyl)phosphines



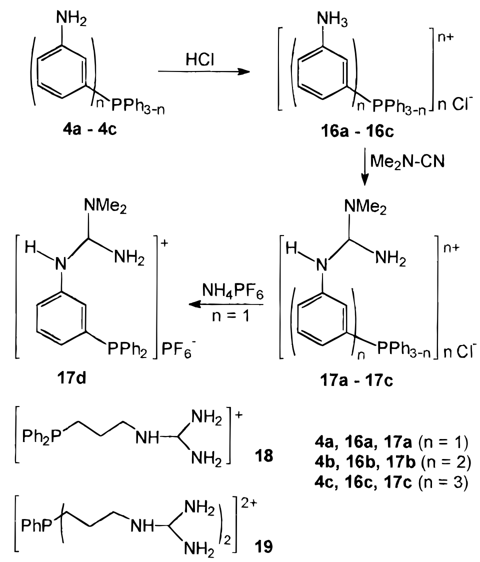
DBPBr = P,P-ditert.butyl phosphetanium bromide

value with those of Ph_2PCl ($\delta P = 81.5$ ppm),[21] (2,4,6-$i\mathrm{Pr}_3C_6H_2$)PhPCl ($\delta P = 77.2$ ppm)[22] and (3-F-C_6H_4)$_2$PCl ($\delta P = 74.7$ ppm).[21] Reduction of the chlorophosphine **6a** in the mixture obtained as above with $LiAlH_4$ yielded **8** ($\delta P = -38.8$ ppm, $^1J_{PH} = 220$ Hz), which could be separated from **2b** and $PhPH_2$ (formed by reduction of excess $PhPCl_2$) by fractionated vacuum distillation. Under these conditions, however, the protecting $SiMe_3$ groups were partially removed as indicated by the ^{1}H NMR spectrum. For a complete deprotection, **8** was treated with methanol at ambient temperature, **7** ($\delta P = -39.6$ ppm, $^1J_{PH} = 220$ Hz) being formed in moderate yield.

The secondary (aminophenyl)phosphine **7** or its *N*-silyl derivative **8** can profitably be used as building blocks for the syntheses of *m*-aminophenyl-substituted chiral bidentate phosphines which are hardly accessible by other routes. Thus, free radical initiated addition of diphenylvinylphosphine[23] to **8** gave the ditertiary phosphine **10** containing a protected amino group (Scheme 3). When **10** was deprotected with an ethereal solution of HCl, the free amino derivative **11** was formed. If **7** was treated with 1 equiv of *n*-BuLi, the amino group is deprotonated primarily as indicated by the δP value of the intermediate ($\delta P = -39.8$ ppm, $^1J_{PH} = 213$ Hz) obtained, which is almost identical to that of the starting material **7** ($\delta P = -39.6$ ppm, $^1J_{PH} = 220$ Hz). Reaction of this intermediate with trimethylchlorosilane yields **12** ($\delta P = -40.2$ ppm, $^1J_{PH} = 214.2$ Hz) which can be metallated with *n*-BuLi, the lithium phosphide **13** ($\delta P = -26.6$ ppm) being formed. Alkylation of **13** with di-*tert*-butylphosphetanium bromide[24a] or coupling with 1,3-dibromopropane yields the ditertiary phosphines **14** or **15**, respectively, after deprotection of the amino group with methanol.

For the syntheses of the guanidinium phosphines **17a**–**c**, the corresponding *m*-aminophenyl derivatives **4a**–**c** were treated with equivalent amounts of ethereal or aqueous HCl solution. The HCl adducts **16a**–**c** formed

Scheme 4. Transformation of (*m*-Aminophenyl)phosphines to the Guanidinium Phosphines



thereby were isolated and identified by NMR spectroscopy. Their phosphorus chemical shifts (δP) were almost identical to those of the neutral compounds, indicating that protonation occurred preferably on the amino groups (Scheme 4) and that the formation of phosphonium salts may be less important.[25] The differences in the δP values between arylphosphines and their HCl or HBr adducts are, however, only within a few ppm (e.g., Ph_3P $\delta P = -6.0$; $Ph_3PH^+Br^-$ $\delta P = -3.1$ ppm).[25a] The analysis of the $^{13}C\{^1H\}$ NMR spectra of **16a**–**c** indicates that all of the amino groups are protonated. The δC values of C2, C4, and C6 are shifted lowfield by ca. 10 ppm while the resonances of the *ipso*-carbon atoms C3 (N) appear about 15 ppm highfield compared with the corresponding values in neutral **4a**–**c**.

(22) Bitterer, F.; Stelzer, O. Unpublished results.
(23) Berlin, K. D.; Butler, G. B. *J. Org. Chem.* **1961**, *26*, 2537. Rabinowitz, R.; Pellon, J. *J. Org. Chem.* **1961**, *26*, 4623.
(24) (a) Brauer, D. J.; Ciccu, A. J.; Hessler, G.; Stelzer, O. *Chem. Ber.* **1992**, *125*, 1987. (b) Tepper, M.; Machnitzki, P.; Stelzer, O. Unpublished results.
(25) (a) Grim, S. O.; Yankowsky, A. W. *J. Org. Chem.* **1977**, *42*, 1236. (b) Davis, M. A. *J. Org. Chem.* **1967**, *32*, 1161. Olah, G. A.; McFarland, C. W. *J. Org. Chem.* **1969**, *34*, 1832.

The introduction of the guanidinium group was achieved by making use of the well-established addition of anilinium salts to cyanamides.[10,26] Thus, reaction of **16a**−**c** with excess dimethylcyanamide at elevated temperatures gave the guanidinium phosphines **17a**−**c** in high yields. As expected, their δP values do not differ significantly from those of **4a**−**c** and **16a**−**c**. Further evidence for the successful conversion of **16a**−**c** into guanidines is provided by the appearance of resonances at δC = 155.4 (**17a**), 156.4 (**17b**), and 157.5 ppm (**17c**) or δC = 38.4 (**17a**), 38.2 (**17b**), and 39.5 ppm (**17c**) in the $^{13}C\{^1H\}$ NMR spectra which may be assigned to the guanidinium carbon atoms[27] or the NMe_2 groups, respectively.

While the guanidinium phosphines **17a**−**c** are insoluble in most organic solvents, they readily dissolve in water, methanol, and ethanol, their solubilities in water being dependent on the counterion. Thus, while **17a** dissolves readily in water, its hexafluorophosphate (**17d**), obtained by a metathesis reaction with ammonium hexafluorophosphate, is quite insoluble in this solvent. The same applies for the iodide of **17b**, obtained from $PhPH_2$ by a P−C coupling reaction,[24b] which is much less soluble in water than the chloride.

Under aerobic conditions, the solutions of the guanidinium phosphines **17b** and **17c**, with chloride or acetate as counterions are much more stable toward oxidation to the phosphine oxide stage when compared to those of the anionic TPPTS ligand. This is a particularly advantageous feature for the preparation and durability of water soluble transition metal complexes employed as *in situ* formed catalysts for palladium complex promoted C−C cross-coupling reactions.[28]

In fact, a stock catalyst solution obtained by mixing palladium acetate (100 μmol) with 500 μmol of the phosphine ligands **17b** and **17c** in water gave no evidence of palladium precipitation and remained catalytically active in model C−C couplings over several months when stored at 4 °C (see below). The prototypical example of a Castro−Stephens coupling[29] between iodobenzoate and *N*-(trifluoroacetyl)propargylamine in homogeneous aqueous solution (H_2O/acetonitrile 50:50 to 70:30) after addition of a premixed catalyst solution of one of the Pd ligands **17b** or **17c** (5−10 mol % Pd), respectively, showed clean and quantitative conversion to the cross-coupled product within a few hours at slightly elevated temperatures (35−50 °C) (Figure 1). Similar reactions were

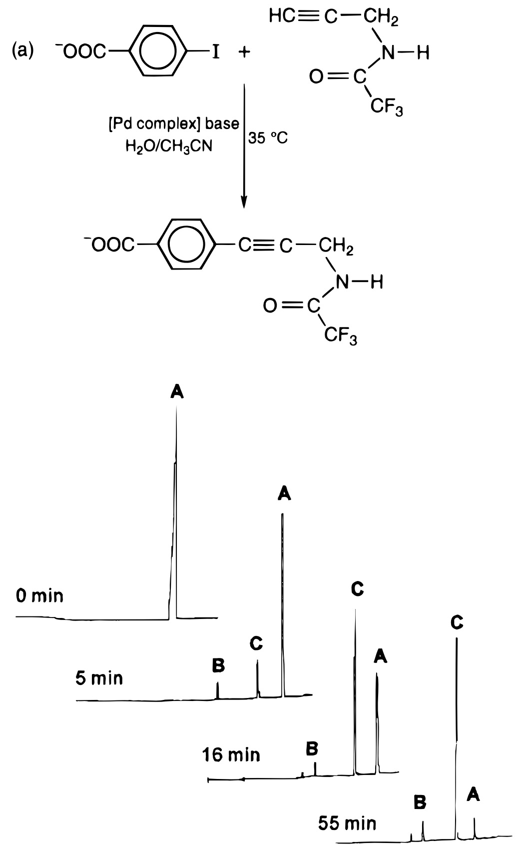


Figure 1. HPLC analysis (detection UV_{254}) of the Castro−Stephens coupling (a) in H_2O/CH_3CN 70:30 catalyzed by 5 mol % [palladium−guanidinophosphine **17b**] complex and 10 mol % CuI at 35 °C with 200 mol % triethylamine. Peak identification: A = iodobenzoate; B = Pd complexes/ligand; C = cross-coupled product.

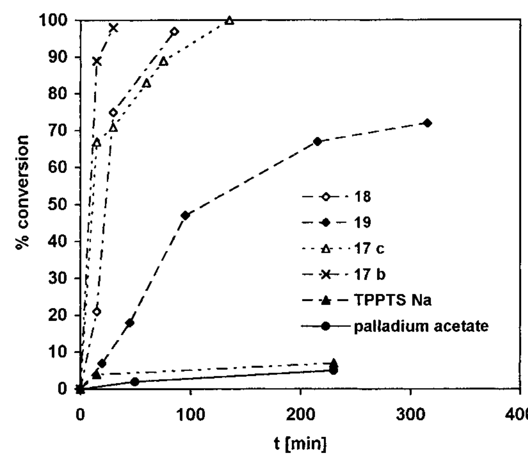


Figure 2. Kinetics of a Castro−Stephens coupling (reaction a, Figure 1) catalyzed by the various palladium−phosphine ligand complexes (5 mol % Pd, 10 mol % CuI) in H_2O/CH_3CN 1:1, T = 35 °C, 200 mol % triethylamine.

observed with free propargylamine or propiolic acid as alkyne substrates. Copper(I) iodide (10 mol %) promoted the rate but was not vital to the success of these C−C bond formations. Reaction pace, however, was very sensitive to the phosphine ligand used. Figure 2 illustrates that the conversion was very sluggish with the anionic TPPTS ligand (**A**), which barely exceeded the efficiency of the simple Pd acetate salt promoted background reaction.

(26) Rasmussen, C. R.; Villani, F. J.; Reynolds, B. E.; Plampin, J. N.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Howse, R. M.; Molinari, A. J. *Synthesis* **1988**, 460. Kämpf, A. *Chem. Ber.* **1904**, *37*, 1681.

(27) (a) Kalinowski, H. O.; Berger, S.; Braun, S. *^{13}C-NMR Spectroscopy*; Georg Thieme Verlag: Stuttgart, New York, 1984; p 220. (b) Cameron, D. G.; Hudson, H. R.; Pianka, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *83*, 21.

(28) For recent examples for Pd-catalyzed C−C connections in water, see: (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (c) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletskaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897. (d) Roshchin, A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125. (e) Diminnie, J.; Metts, S.; Parsons, E. J. *Organometallics* **1995**, *14*, 4023. (f) Genêt, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 1443. (g) Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, *36*, 3111. (h) Kiji, J.; Okano, T.; Hasegawa, T. *J. Mol. Catal. A: Chem.* **1995**, *97*, 73. (i) Sengupta, S.; Bhattacharyya, S. *Tetrahedron Lett.* **1995**, *36*, 4475. (j) Amatore, Ch.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829.

(29) (a) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 3313. (c) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071.

On the contrary, all of the cationic guanidinophosphines formed quite active catalysts with the biscationic ligand **17b** exhibiting the highest activity. With this complex system the quantitative coupling of *p*-iodobenzoic acid and propiolic acid was achieved in 30 min at 35 °C using 5 mol % Pd complex and 10 mol % CuI cocatalyst in 30 vol % acetonitrile in water. The triaryl ligands **17b** and **17c** were at least equal or even outperformed cationic aryl alkyl guanidino phosphine ligands (e.g. **18/19**) in any of these reactions.[9]

The molar ratio of the substrates had no effect on the rate or on the product distribution even when the triple-bonded reaction partner was used in 500 mol % excess. Thus, homocoupling of the alkynic components which severely weakened cross-coupling yields for phenylacetylene derivatives[9] was totally absent when aliphatic alkynes were employed as substrates.

The reactions required stoichiometric amounts of base but neither the chemical nature (triethylamine or K_2CO_3 were equally effective) nor an excess appeared to be crucial or helpful. Furthermore, the organic solvent additive (CH_3CN or DMF) was only of minor influence, although it was observed that the reaction rate was more sensitive to the alteration of the concentration of DMF.

In summary, the cationic guanidino phosphines **17a**−**c** are suitable ligands for forming water soluble palladium complex catalysts which are durable and active in very mild, clean, and quantitative intermolecular C−C connections in homogeneous aqueous solution. A bright perspective of these catalytic systems in bioconjugation reactions can be readily predicted.

Experimental Section

General. ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra were recorded at 400.1, 100.6, and 161.9 or 36.2 MHz. Product analysis and kinetics were obtained by HPLC. The kinetic results refer to peak height ratios measured at $\lambda = 254$ nm in standard HPLC runs, defining conversion as the ratio [product/product + starting material] × 100. The eluents contained 30 mM H_3PO_4 and 30 mM $NaClO_4$ in addition to the organic modifier. All coupling products were isolated and characterized by standard ^{1}H/^{13}C NMR techniques. For higher order spectra N_{CP} is defined as $|^1J_{CP} + {}^nJ_{CP}|$.

Chemicals. The chlorophosphines Cl(Ph)PNR$_2$ (R = Me, Et) were prepared according to the literature methods[21] by the reaction of $PhPCl_2$ with the corresponding silylamines (Me_3SiNR_2). Diphenylvinylphosphine[23] was obtained from Ph_2PCl and vinylmagnesium chloride. *P,P*-Di-*tert*-butylphosphetanium bromide[24a] was prepared by treatment of *t*-Bu$_2$PSiMe$_3$ with 1,3-dibromopropane. (3-[*N,N*-Bis(trimethylsilyl)amino]phenyl)magnesium chloride (**1**) was purchased from Aldrich. Other solvents and reagents were of guaranteed grade and distilled before use.

Synthesis of 2a. To a 1.0 M THF solution of (3-[*N,N*-bis(trimethylsilyl)amino]phenyl)magnesium chloride (**1**) (100 mL; 0.10 mol) was added 22.1 g (0.10 mol) of diphenylchlorophosphine dissolved in 100 mL THF at ambient temperature. After 2 h of stirring, all volatiles were removed in vacuo (20 °C, 0.1 mbar). The residue was extracted with diethyl ether (150 mL). From the oily residue remaining after removal of the solvents, pure **2a** was obtained by short path distillation in vacuo (140 °C; 0.01 mbar).

Diphenyl([*N,N*-bis(trimethylsilyl)amino]phenyl)phosphine (2a): 66% yield; ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 18 H), 6.5−7.2 (m, 14 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ −6.1; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 137.1 (J_{CP} = 11.0 Hz), 128.5 (J_{CP} = 8.8 Hz), 148.2 (J_{CP} = 7.3 Hz), 130.3, 129.5, 135.1 (J_{CP} = 16.1 Hz), 137.4 (J_{CP} = 11.0 Hz), 133.6 (J_{CP} = 19.8 Hz), 128.5, 128.2, 2.1 (Si*Me*$_3$); MS (EI) *m/z* 421 (M$^+$, 26), 406 (M$^+$ − CH$_3$, 27), 221 (C$_6$H$_4$N(SiMe$_3$)$_2$ − CH$_3$, 6), 185 (Ph$_2$P, 15), 73 (SiMe$_3$, 100). Anal. Calcd for $C_{24}H_{32}NPSi_2$: C, 68.36; H, 7.65. Found: C, 68.29; H, 7.79.

Synthesis of 2b. In a manner analogous to that given above, to 160 mL (0.16 mol) of **1** (1.0 M THF solution) was added 14.3 g (0.08 mol) phenyldichlorophosphine in 100 mL of THF at ambient temperature. After a similar workup procedure, **2b** was obtained by short path distillation (160 °C, 0.01 mbar).

Phenylbis([*N,N*-bis(trimethylsilyl)amino]phenyl)phosphine (2b): 72% yield; ^{1}H NMR (CD_2Cl_2) δ 0.1 (s, 36 H), 6.5−7.3 (m, 13 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ −6.5; ^{13}C{^{1}H} NMR (CD_2Cl_2) δ 135.7 (J_{CP} = 12.1 Hz), 127.2 (J_{CP} = 23.3 Hz), 146.5 (J_{CP} = 6.1 Hz),[30] 133.2 (J_{CP} = 15.2 Hz), 136.1 (J_{CP} = 11.7 Hz), 131.7 (J_{CP} = 19.3 Hz), 128.5, 0.0 (Si*Me*$_3$); MS (EI) *m/z* 580 (M$^+$, 6), 472 (M$^+$ − C$_6$H$_5$, −2 CH$_3$, −H, 7), 221 (C$_6$H$_4$N(SiMe$_3$)$_2$ − CH$_3$, 10), 73 (SiMe$_3$, 100). Anal. Calcd for $C_{30}H_{49}N_2PSi_4$: C, 62.01; H, 8.50. Found: C, 62.11; H, 8.43.

Synthesis of 2c. Phosphorus trichloride (10.3 g, 0.075 mol) in 100 mL of THF was reacted with 250 mL (0.25 mol) of a 1.0 M THF solution of **1** at room temperature. The residue remaining after evaporation of the reaction mixture was extracted with petroleum ether (200 mL) and water (50 mL). The organic phase was separated by decantation and dried over magnesium sulfate. Compound **2c** was obtained as a viscous oily liquid after removing the solvent in vacuo (20 °C, 0.1 mbar).

Tris([*N,N*-bis(trimethylsilyl)amino]phenyl)phosphine (2c): 93 % yield; ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 54 H), 6.6−7.2 (m, 12 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ −6.2; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 137.4 (J_{CP} = 11.7 Hz), 128.4 (J_{CP} = 8.8 Hz), 148.2 (J_{CP} = 6.6 Hz), 130.2, 129.6, 134.9 (J_{CP} = 15.4 Hz), 2.1 (Si*Me*$_3$); MS (EI) *m/z* 740 (M$^+$, 38), 739 (M$^+$ − H, 54), 503 (M$^+$ − H, −C$_6$H$_4$N(SiMe$_3$)$_2$, 6), 73 (SiMe$_3$, 100). Anal. Calcd for $C_{36}H_{66}N_3PSi_6$: C, 58.40; H, 8.98; N, 5.68. Found: C, 58.04; H, 8.95; N, 6.10.

Syntheses of 4a−c. General Procedure. The phosphine ligands **2a** (20.0 g, 0.047 mol), **2b** (12.5 g, 0.022 mol), or **2c** (7.4 g, 0.01 mol), respectively, were dissolved in 100 mL of pure methanol (**4a** or **4b**) or a mixture of methanol (15 mL) and THF (10 mL) (**4c**) and heated at reflux for 8−15 h. Compounds **4a** and **4b** precipitated from the reaction mixtures. They were collected on a sintered glass funnel and dried in vacuo (20 °C, 0.1 mbar). For the isolation of **4c**, all volatiles were removed in vacuo and the remaining residue was washed with petroleum ether 40:60 (20 mL). After drying at 20 °C, 0.1 mbar, it was obtained as a colorless solid.

Diphenyl(3-aminophenyl)phosphine (4a): 76% yield; ^{1}H NMR (CD_2Cl_2) δ 3.6 (s, br, 2 H), 6.6−7.4 (m, 14 H); ^{31}P{^{1}H} NMR (CD_2Cl_2) δ −3.1; ^{13}C{^{1}H} NMR (CD_2Cl_2) δ 137.5 (J_{CP} = 11.7 Hz), 119.7 (J_{CP} = 20.5 Hz), 146.9 (J_{CP} = 8.1 Hz), 115.3, 129.4 (J_{CP} = 8.1 Hz), 123.5 (J_{CP} = 19.8 Hz), 138.1 (J_{CP} = 10.3 Hz), 133.7 (J_{CP} = 19.8 Hz), 128.5 (J_{CP} = 6.6 Hz), 128.6; IR ν (cm^{-1}) 3439, 3356; MS (EI) *m/z* 277 (M$^+$, 100), 198 (M$^+$ − C$_6$H$_5$, −2H, 48), 183 (Ph$_2$P − 2H, 31), 92 (C$_6$H$_4$NH$_2$, 5). Anal. Calcd for $C_{18}H_{16}NP$: C, 77.97; H, 5.82; N, 5.05. Found: C, 78.07; H, 5.88; N, 5.25.

Phenylbis(3-aminophenyl)phosphine (4b): 84% yield; ^{31}P{^{1}H} NMR (DMSO-*d*$_6$) δ 0.2; ^{13}C{^{1}H} NMR (DMSO-*d*$_6$) δ 137.1 (J_{CP} = 9.5 Hz), 118.5 (J_{CP} = 22.0 Hz), 148.6 (J_{CP} = 8.8 Hz), 114.4, 128.9 (J_{CP} = 8.1 Hz), 120.7 (J_{CP} = 19.1 Hz), 137.7 (J_{CP} = 12.5 Hz), 133.2 (J_{CP} = 19.1 Hz), 128.3 (J_{CP} = 6.6 Hz), 128.4; IR ν (cm^{-1}) 3445, 3367; MS (EI) *m/z* 292 (M$^+$, 100), 291 (M$^+$ − H, 14), 213 (M$^+$ − 2H, −C$_6$H$_5$, 28), 198 (M$^+$ − C$_6$H$_4$NH$_2$, − 2H, 57). Anal. Calcd for $C_{18}H_{17}N_2P$: C, 73.96; H, 5.86; N, 9.58. Found: C, 73.89; H, 5.87; N, 9.21.

Tris(3-aminophenyl)phosphine (4c): 91% yield; ^{1}H NMR (DMSO-*d*$_6$) δ 4.0 (s, br, 6 H), 6.3−7.2 (m, 12 H); ^{31}P{^{1}H} NMR (DMSO-*d*$_6$) δ 1.1; ^{13}C{^{1}H} NMR (DMSO-*d*$_6$) δ 138.6 (J_{CP} = 9.7 Hz), 119.6 (J_{CP} = 22.5 Hz), 149.3 (J_{CP} = 8.7 Hz), 115.1, 129.6 (J_{CP} = 7.5 Hz), 121.7 (J_{CP} = 18.2 Hz); IR ν (cm^{-1}) 3470, 3367; MS (EI) *m/z* 307 (M$^+$, 100); 306 (M$^+$ − H, 14); 214 (M$^+$ − C$_6$H$_4$NH$_2$, − H, 16). Anal. Calcd for $C_{18}H_{18}N_3P$: C, 70.33; H, 5.91; N, 13.68. Found: C, 70.90; H, 6.21; N, 14.00.

(30) Overlap of three resonances in the range for δC of 126.8−126.4 ppm.

Syntheses of 5a−c. (Dimethylamino)phenylchlorophosphine (26.3 g, 0.14 mol) or (diethylamino)phenylchlorophosphine (17.3 g, 0.08 mol), respectively, dissolved in THF (100 mL) were added to a solution of 140 mL (0.14 mol) or 80 mL (0.08 mol) of (3-[*N*,*N*-bis(trimethylsilyl)amino]phenyl)magnesium chloride (1.0 M) in THF and stirred for 16 h at ambient temperature. The residue obtained after evaporation of the reaction mixture in vacuo was extracted with petroleum ether 40:60 (150 mL). After the filtrate was evaporated to dryness and the remaining oily residue was fractionated in vacuo at 150 or 160 °C, respectively, using a short path distillation apparatus, **5a** and **5b** were obtained as colorless liquids. For the preparation of **5c**, methanol (30 mL) was added to the solutions of 50 g (0.13 mol) of **5a** or 22.5 g (0.054 mol) of **5b**, respectively, in 50 or 30 mL of toluene and the reaction mixtures were heated at reflux for 10 min or 12 h, respectively. The oily residue obtained after removal of all volatiles was fractionated in vacuo at 120 °C, 0.1 mbar.

(3-[*N*,*N*-Bis(trimethylsilyl)amino]phenyl)(dimethylamino)phenylphosphine (5a): 94% yield; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 64.1; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.5 (J_{CP} = 16.1 Hz), 128.2 (J_{CP} = 14.0 Hz), 147.8 (J_{CP} = 6.6 Hz), 130.3, 127.2, 133.5 (J_{CP} = 17.6 Hz), 138.9 (J_{CP} = 13.9 Hz), 131.8 (J_{CP} = 19.1 Hz), 128.1 (J_{CP} = 5.1 Hz), 127.8, 2.1 (Si*Me*3), 41.8 (N*Me*2) (J_{CP} = 14.7 Hz); MS (EI) *m/z* 388 (M^+, 36), 330 ($M^+ - SiMe_2$, 14), 311 ($M^+ - C_6H_5$, 9), 152 ($PhPNMe_2$, 14), 73 ($SiMe_3$, 100). Anal. Calcd for $C_{20}H_{33}N_2PSi_2$: C, 61.81; H, 8.56. Found: C, 61.88; H, 8.58.

(3-[*N*,*N*-Bis(trimethylsilyl)amino]phenyl)(diethylamino)phenylphosphine (5b): 97% yield; ^1H NMR ($CDCl_3$) δ 0.0 (s, 18 H), 0.9 (t, 6 H, $^3J_{HH}$ = 7.7 Hz), 3.0 (q, 4 H, $^3J_{HH}$ = 7.7 Hz), 6.8−7.4 (m, 9 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 60.9; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 140.2 (J_{CP} = 1.5 Hz), 128.2 (J_{CP} = 3.7 Hz), 147.7 (J_{CP} = 5.9 Hz), 130.1, 127.2, 133.5 (J_{CP} = 18.3 Hz), 140.8, 131.7 (J_{CP} = 19.1 Hz), 128.0 (J_{CP} = 2.0 Hz), 127.2, 2.1 (Si*Me*3), 44.2 (N*CH*2CH3) (J_{CP} = 15.4 Hz), 14.5 (NCH2*CH*3) (J_{CP} = 2.9 Hz); MS (EI) *m/z* 416 (M^+, 20), 344 ($M^+ - NEt_2$, 10), 180 ($PhPNEt_2$, 6), 73 ($SiMe_3$, 100). Anal. Calcd for $C_{22}H_{37}N_2PSi_2$: C, 63.41; H, 8.95. Found: C, 63.59; H, 8.72.

(3-[*N*,*N*-Bis(trimethylsilyl)amino]phenyl)methoxyphenylphosphine (5c): 81% yield; ^1H NMR ($CDCl_3$) δ 0.0 (s, 18 H), 3.6 (d, 3 H, $^3J_{PH}$ = 14.0 Hz), 6.6−7.8 (m, 9 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 116.5; $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 141.2 (J_{CP} = 4.4 Hz), 128.4 (J_{CP} = 8.1 Hz), 148.0 (J_{CP} = 7.3 Hz), 126.3, 130.9 (J_{CP} = 6.6 Hz), 131.7 (J_{CP} = 19.8 Hz), 142.0 (J_{CP} = 2.7 Hz), 129.5 (J_{CP} = 15.4 Hz), 128.2 (J_{CP} = 6.6 Hz), 125.2, 2.0 (Si*Me*3), 56.5 (O*Me*) (J_{CP} = 17.6 Hz); MS (EI) *m/z* 375 (M^+, 21), 360 ($M^+ - CH_3$, 13), 73 ($SiMe_3$, 100). Anal. Calcd for $C_{19}H_{30}NOPSi_2$: C, 60.76; H, 8.05. Found: C, 60.92; H, 8.05.

Reduction of 5c with $LiAlH_4$. Synthesis of 8. To a suspension of 1.8 g (47.4 mmol) of $LiAlH_4$ in diethyl ether (200 mL) was added a solution of 17.5 g (46.6 mmol) of **5c** at ambient temperature, and the reaction mixture was stirred for 3 h. After dropwise addition of 20 mL of water within a period of 1 h, the organic phase was separated and evaporated to dryness in vacuo (20 °C, 0.01 mbar). According to the $^{31}P\{^1H\}$ NMR spectrum of a sample, the residue contained the desired secondary phosphine **8** in addition to the diphosphine **9** in ca. 1:2.3 ratio. In order to reduce **9**, the reaction mixture was dissolved in methyl *tert*-butyl ether (300 mL) and treated with 15.0 g (0.65 mol) of sodium at reflux for 28 h. After cooling the solution to room temperature, excess sodium was separated by decantation. Ethanol (15 mL) and water (50 mL) were added to the solution. The organic layer was separated and evaporated under reduced pressure. Distillation of the crude product gave the secondary phosphine **8** as a colorless air-sensitive liquid.

(3-[*N*,*N*-Bis(trimethylsilyl)amino]phenyl-phenyl)phosphine (8): 46% yield; ^1H NMR (CD_2Cl_2) δ 0.0 (s, 18 H), 5.2 (d, 1 H, $^1J_{PH}$ = 217.1 Hz), 6.6−7.5 (m, 9 H); $^{31}P\{^1H\}$ NMR (CD_2Cl_2) δ −38.8 ($^1J_{PH}$ = 217.1 Hz); $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 135.5 (J_{CP} = 10.3 Hz), 128.9 (J_{CP} = 5.1 Hz), 148.5 (J_{CP} = 6.6 Hz), 130.5, 129.8, 134.9 (J_{CP} = 10.3 Hz), 135.9 (J_{CP} = 15.4 Hz), 133.9 (J_{CP} = 16.9 Hz), 128.5 (J_{CP} = 1.5 Hz), 128.7, 2.1 (Si*Me*3); MS (EI) *m/z* 345 (M^+, 19), 330 ($M^+ - CH_3$, 31), 73 (Me_3Si, 100). Anal. Calcd for $C_{18}H_{28}NPSi_2$: C, 62.56; H, 8.17. Found: C, 62.50; H, 8.25.

Preparation of 7 from $PhPCl_2$. To a solution of 38.7 g (0.22 mol) of phenyldichlorophosphine in THF (300 mL) was added 195 mL (0.195 mol) of (3-[*N*,*N*-bis(trimethylsilyl)amino]phenyl)magnesium chloride dropwise at −50 °C within 1 h. After the addition was complete, the reaction mixture was allowed to warm to 20 °C and stirred for 2 h at this temperature. The residue obtained after the solvent was removed contained, in addition to unreacted phenyldichlorophosphine, the tertiary phosphine **2b** (δP = 80.5 ppm) and the chlorophosphine **6a** in a 1:1 ratio as indicated by the $^{31}P\{^1H\}$ NMR spectrum of a sample. For the reduction of **6a** (δP = −6.5 ppm), the reaction mixture was dissolved in diethyl ether (300 mL). This solution was added at 0 °C within 2 h to a suspension of 7.6 g (0.20 mol) of $LiAlH_4$ and stirred for 2 h. After hydrolytic workup of the reaction mixture (by addition of 20 mL of water), the organic phase was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure. Evaporation of the crude product gave phenylphosphine (70 °C, 0.1 mbar), and subsequent short-path distillation at 140 °C yielded a fraction which, according to the ^1H NMR spectrum, contained **8** in addition to the deprotected secondary phosphine **7**. In order to get an uniform product, the mixture was stirred for 1 h in methanol. After removing all volatiles at 50 °C, 0.1 mbar, the unprotected phosphine **7** was obtained.

Phenyl(3-aminophenyl)phosphine (7): 21% yield; $^{31}P\{^1H\}$ NMR (CD_2Cl_2) δ −39.6 ($^1J_{PH}$ = 220 Hz); $^{13}C\{^1H\}$ NMR (CD_2Cl_2) δ 134.4 (J_{CP} = 9.5 Hz), 119.9 (J_{CP} = 16.9 Hz), 146.1 (J_{CP} = 7.3 Hz), 115.1, 129.1 (J_{CP} = 7.3 Hz), 123.6 (J_{CP} = 16.9 Hz), 135.0 (J_{CP} = 8.8 Hz), 133.5 (J_{CP} = 16.9 Hz), 128.2 (J_{CP} = 5.9 Hz), 128.0; MS (EI) *m/z* 201 (M^+, 58), 198 ($M^+ - 3H$, 12), 124 ($M^+ - C_6H_5$, 26), 109 (PhPH, 100), 92 ($C_6H_4NH_2$, 35). Anal. Calcd for $C_{12}H_{12}NP$: C, 71.63; H, 6.01. Found: C, 71.58; H, 6.20.

Synthesis of Bidentate 3-Aminophenyl-Substituted Phosphines. Preparation of 10 and 11. A solution of 3.0 g (8.7 mmol) of **8** and 1.84 g (8.7 mmol) of diphenylvinylphosphine in toluene (20 mL) was stirred at 70 °C for 4 d. In order to initiate and continue the free radical addition, aliquots of AIBN (ca. 20 mg) were added to the reaction mixture every 24 h. After the solvent was removed in vacuo, **10** was obtained as a colorless viscous liquid. For deprotection, the product obtained above was dissolved in methanol. After an ethereal solution of HCl (1 mL, 1.65 M) was added, **11** precipitated as a colorless solid from the reaction mixture. It was isolated by filtration on a glass funnel and dried in vacuo.

(2-(Diphenylphosphino)ethyl)([3-*N*,*N*-bis(trimethylsilyl)amino]phenyl)phenylphosphine (10): 83% yield; $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ −11.0, −11.4 ($^3J_{PP}$ = 33.1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.8 (J_{CP} = 11.2 Hz), 128.3 (J_{CP} = 16.3 Hz), 148.6 (J_{CP} = 7.1 Hz), 130.9, 129.0, 135.0 (J_{CP} = 17.4 Hz), 139.0 (J_{CP} = 13.1 Hz), 133.6 (J_{CP} = 19.2 Hz), 129.0 (J_{CP} = 11.6 Hz), 128.7, 24.6−24.2 (m), 138.7 (J_{CP} = 12.3 Hz), 133.3 (J_{CP} = 18.1 Hz), 128.8 (J_{CP} = 6.3 Hz), 128.8, 2.6 (Si*Me*3); MS (EI) *m/z* 557 (M^+, 35), 183 ($Ph_2P - 2H$, 13), 73 ($SiMe_3$, 100). Anal. Calcd for $C_{32}H_{41}NP_2Si_2$: C, 68.90; H, 7.41. Found: C, 68.95; H, 7.45.

(2-(Diphenylphosphino)ethyl)(3-aminophenyl)phenylphosphine (11): 76% yield; ^1H NMR ($CDCl_3$) δ 2.4 (m, 4 H), 2.8 (s, br, 2 H), 6.9−7.5 (m, 19 H); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ −10.6, −11.2 ($^3J_{PP}$ = 33.4 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 139.6 (J_{CP} = 12.2 Hz), 120.8 (J_{CP} = 17.3 Hz), 148.0 (J_{CP} = 7.1 Hz), 117.4, 130.7 (J_{CP} = 7.1 Hz), 124.3 (J_{CP} = 17.3 Hz), 140.1 (J_{CP} = 11.2 Hz), 134.1 (J_{CP} = 16.3 Hz), 130.1 (J_{CP} = 8.1 Hz), 130.1, 25.2 (N_{CP} = 22.4 Hz), 25.3 (N_{CP} = 23.4 Hz) (CH_2CH_2), 139.4 (N_{CP} = 17.3 Hz), 134.1 (J_{CP} = 18.3 Hz), 129.8 (J_{CP} = 8.1 Hz), 129.9; MS (EI) *m/z* 413 (M^+, 80), 385 ($M^+ - C_2H_4$, 34), 185 (Ph_2P, 34), 183 ($Ph_2P - 2H$, 100). Anal. Calcd for $C_{26}H_{25}NP_2$: C, 75.53; H, 6.09; N, 3.39. Found: C, 75.18; H, 6.40; N, 3.16.

Preparation of 14. To a solution of 4.62 g (23.0 mmol) of **7** in THF (100 mL) was added 15 mL (23.0 mmol) of 1.6 N *n*-BuLi at −70 °C. The reaction mixture was allowed to warm to -40 °C, and 2.50 g (23.0 mmol) of Me_3SiCl were added at this temperature. After cooling the solution to −70 °C, the protected secondary phosphine was metallated with *n*-BuLi

(15 mL; 23.0 mmol). To the solution of the lithium phosphide formed was added 6.13 g (23.0 mmol) of 1,1-di-*tert*-butylphosphetanium bromide. After 18 h of stirring at ambient temperature, all volatiles were removed under reduced pressure. The residue was extracted with petroleum ether 40:60, and the extracts were evaporated in vacuo giving a yellow viscous liquid. For deprotection, the crude product (δP = 24.3 (P_A), −18.3 ppm (P_B)) was dissolved in methanol (20 mL) at 20 °C. Volatile material was removed under reduced pressure to give **14** as a viscous yellow liquid.

(3-(Di-*tert*-butylphosphino)propyl)(3-aminophenyl)-phenylphosphine (14): 43% yield; ^{1}H NMR (CD_2Cl_2) δ 1.1 (d, 18 H, $^3J_{PH}$ = 11.0 Hz); 1.3−1.7 (m 6 H); 6.6−7.4 (m, 9 H); ^{31}P{^{1}H} NMR (CD_2Cl_2) δ 25.3 (P(*t*-Bu)), −16.5 (P(Ph)); ^{13}C{^{1}H} NMR (CD_2Cl_2) δ 138.7 (J_{CP} = 14.2 Hz), 118.0 (J_{CP} = 19.5 Hz), 146.0 (J_{CP} = 7.5 Hz), 114.3, 128.4 (J_{CP} = 7.2 Hz), 121.6 (J_{CP} = 18.3 Hz), 139.2 (J_{CP} = 12.7 Hz), 131.9 (J_{CP} = 18.3 Hz), 127.5 (J_{CP} = 6.5 Hz), 26.1−25.6 (m), 22.1 (J_{CP} = 21.4, 12.3 Hz), 30.3 (J_{CP} = 20.9 Hz), 28.7 (J_{CP} = 13.8 Hz) ($CH_2CH_2CH_2$); MS (EI) *m/z* 330 (M^+ − C_4H_9, 100), 274 (M^+ − C_4H_9, −C_4H_8, 44), 273 (M^+ − 2C_4H_9, 14), 198 ($PhPC_6H_4NH_2$ − 2H, 17). Anal. Calcd for $C_{23}H_{35}NP_2$: C, 71.29; H, 9.10; N, 3.62. Found: C, 70.81; H, 8.97; N, 3.20.

Preparation of 15. The solution of 2.17 g (10.8 mmol) of **7** in diethyl ether (20 mL) was treated at −60 °C with 6.3 mL (10.8 mmol) of *n*-BuLi dissolved in *n*-hexane. After 30 min, 1.17 g (10.8 mmol) of Me_3SiCl was added at −40 °C with stirring. For the metallation of the intermediate, protected secondary phosphine **12** 6.3 mL (10.8 mmol) of *n*-BuLi were added at −60 °C and subsequently 1.09 g (5.4 mmol) of 1,3-dibromopropane. The reaction mixture was allowed to warm and was stirred for 72 h at ambient temperature. The residue remaining after evaporation was treated with a mixture of dichloromethane (20 mL) and water (5 mL). The organic phase was separated, dried over magnesium sulfate, and filtered, and the solvent removed under reduced pressure to give the protected ditertiary phosphine. The protecting groups were removed as for **14**, leaving **15** as a colorless powder.

1,3-Bis[(3-aminophenyl)phenylphosphino]propane (15): 39% yield; ^{1}H NMR (CD_2Cl_2) δ 1.1−1.3 (m, 2 H), 2.1−2.2 (m, 4 H), 3.8 (s, br, 4 H), 6.5−7.5 (m 18H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ −17.2; ^{13}C{^{1}H} NMR (CD_2Cl_2) δ 139.7 (J_{CP} = 14.2 Hz), 119.2 (J_{CP} = 15.3 Hz), 147.2 (J_{CP} = 7.1 Hz), 115.6, 129.6 (J_{CP} = 8.1 Hz), 122.9 (J_{CP} = 19.3 Hz), 140.1 (J_{CP} = 13.2 Hz), 132.1 (J_{CP} = 18.3 Hz), 128.8 (J_{CP} = 7.0 Hz), 128.8, 29.81 (N_{CP} = 25.4 Hz), 29.78 (N_{CP} = 24.4 Hz) (diastereoisomers), 23.08 (J_{CP} = 17.8 Hz), 23.04 (J_{CP} = 17.3 Hz) (diastereoisomers); IR ν (cm^{-1}) 3442, 3356; MS (EI) *m/z* 442 (M^+, 72), 365 (M^+ − C_6H_5, 100), 350 (M^+ − $C_6H_4NH_2$, 85), 123 ($PC_6H_4NH_2$, 35). Anal. Calcd for $C_{27}H_{28}N_2P_2$: C, 73.28; H, 6.38. Found: C, 72.78; H, 6.21.

Preparation of the Guanidinium Phosphines 17a−c. Synthesis of the Anilinium Phosphines 16a−c. To the solutions of **4a** (1.46 g, 5.3 mmol) or **4b** (1.24 g, 4.2 mmol) in dichloromethane (20 mL) or THF (20 mL), respectively, was added 3.5 or 5.1 mL of etheral HCl (1.65 N) with stirring. Compound **16b** was precipitated as an off white solid, which was collected on a fritted glass funnel. For the isolation of **16a**, the solvent was evaporated. The remaining residue crystallized upon addition of a small quantity of diethyl ether. Compounds **16a** and **16b** were dried in vacuo. The anilinium salt **16c** was obtained on treating an aqueous suspension of **4c** (2.75 g, 9.0 mmol) in 100 mL of water with 13.5 mL of hydrochloric acid (2 N). The clear solution was stirred for 30 min at ambient temperature. After the solvent was removed under reduced pressure at 60 °C, **16c** was obtained as a colorless solid.

[Diphenyl(3-aminophenyl)phosphine] hydrochloride (16a): 98% yield; ^{31}P{^{1}H} NMR ($CDCl_3$) δ −5.1; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 141.5 (J_{CP} = 15.7 Hz), 128.6 (J_{CP} = 21.7 Hz), 130.7 (J_{CP} = 7.0 Hz), 124.2, 130.4 (J_{CP} = 7.0 Hz), 136.4 (J_{CP} = 8.7 Hz), 134.3 (J_{CP} = 19.1 Hz), 129.2 (J_{CP} = 6.1 Hz), 129.6; IR ν (cm^{-1}) 2842; MS (EI) *m/z* 277 (M^+ − HCl, 100), 183 (Ph_2P − 2H, 34), 123 ($PC_6H_4NH_2$, 26), 36 ($H^{35}Cl$, 3). Anal. Calcd for $C_{18}H_{17}ClNP$: C, 68.90; H, 5.46; N, 4.46. Found: C, 68.48; H, 5.30; N, 4.15.

[Phenylbis(3-aminophenyl)phosphine] dihydrochloride (16b): 98% yield; ^{31}P{^{1}H} NMR (CD_3OD) δ −3.6; ^{13}C{^{1}H} NMR (CD_3OD) δ 139.8 (J_{CP} = 15.3 Hz), 127.7 (J_{CP} = 18.3 Hz), 131.6 (J_{CP} = 6.1 Hz), 123.9, 130.4 (J_{CP} = 7.1 Hz), 133.9 (J_{CP} = 20.4 Hz), 135.1 (J_{CP} = 11.2 Hz), 134.0 (J_{CP} = 22.4 Hz), 129.0 (J_{CP} = 7.1 Hz), 129.8; IR ν (cm^{-1}) 2820; MS (EI) *m/z* 292 (M^+ − 2HCl, 47), 276 (M^+ − 2HCl, −NH_2, 12), 198 (M^+ − 2HCl, −$C_6H_4NH_2$, − 2H, 100), 123 ($PC_6H_4NH_2$, 11).

[Tris(3-aminophenyl)phosphine] trihydrochloride (16c): 77% yield; ^{31}P{^{1}H} NMR (D_2O) δ −5.3; ^{13}C{^{1}H} NMR (D_2O) δ 137.8 (J_{CP} = 11.2 Hz), 127.4 (J_{CP} = 21.4 Hz), 131.3 (J_{CP} = 9.2 Hz), 124.0, 130.8 (J_{CP} = 7.1 Hz), 133.7 (J_{CP} = 18.3 Hz); IR ν (cm^{-1}) 2856; MS (EI) *m/z* 307 (M^+ − 3HCl, 100), 306 (M^+ − 3HCl, −H, 18), 213 (M^+ − 3HCl, −$C_6H_4NH_2$, − 2H, 80), 38 ($H^{37}Cl$, 60), 36 ($H^{35}Cl$, 100). Anal. Calcd for $C_{18}H_{21}Cl_3N_3P$: C, 51.88; H, 5.08; N, 10.08. Found: C, 51.69; H, 5.73; N, 9.54.

Syntheses of the Guanidinium Phosphines 17a−c. General Procedure. The anilinium phosphines **16a** (2.20 g, 7.9 mmol), **16b** (1.24 g, 4.2 mmol), and **16c** (1.4 g, 4.6 mmol) were added to excess dimethylcyanamide (2.90 g, 41.1 mmol; 1.20 g, 17.1 mmol; or 4.37 g, 62.3 mmol, respectively) and stirred for 12 h at 110 °C. In order to remove excess dimethylcyanamide, the highly viscous reaction mixtures were extracted with ether (30 mL). The guanidinium phosphines were obtained as creme-colored solids which were dried overnight in vacuo.

[Diphenyl(3-(*N*,*N*-dimethylguanidino)phenyl)phosphine] hydrochloride (17a): 92% yield; ^{1}H NMR (D_2O) δ 3.2 (s, 6 H), 5.0 (s, br, 3 H), 7.2−7.7 (m, 14 H); ^{31}P{^{1}H} NMR (CD_3OD) δ −1.2; ^{13}C{^{1}H} NMR (D_2O) δ 139.0 (J_{CP} = 12.2 Hz), 128.1 (J_{CP} = 18.3 Hz), 136.8 (J_{CP} = 8.1 Hz), 124.5, 132.0, 131.0 (J_{CP} = 20.4 Hz), 136.3 (J_{CP} = 10.2 Hz), 133.7 (J_{CP} = 20.3 Hz), 128.9 (J_{CP} = 7.1 Hz), 129.3, 155.4 (*C*N_3), 38.4 (N*Me*$_2$). Anal. Calcd for $C_{21}H_{23}ClN_3P$: C, 65.71; H, 6.04; N, 10.95. Found: C, 65.23; H, 6.34; N, 11.42.

[Phenylbis(3-(*N*,*N*-dimethylguanidino)phenyl)phosphine] dihydrochloride (17b): 91% yield; ^{1}H NMR (CD_3OD) δ 3.2 (s, 12 H), 5.1 (s, br, 6 H), 6.8−8.3 (m, 13 H); ^{31}P{^{1}H} NMR (CD_3OD) δ −0.9; ^{13}C{^{1}H} NMR (CD_3OD) δ 139.7 (J_{CP} = 13.7 Hz), 129.4 (J_{CP} = 19.9 Hz), 137.3 (J_{CP} = 9.0 Hz), 125.2, 130.2 (J_{CP} = 7.1 Hz), 131.9 (J_{CP} = 20.3 Hz), 136.2 (J_{CP} = 10.0 Hz), 134.1 (J_{CP} = 20.8 Hz), 129.0 (J_{CP} = 7.2 Hz), 129.6, 156.4 (*C*N_3), 38.2 (N*Me*$_2$). Anal. Calcd for $C_{24}H_{31}Cl_2N_6P$: C, 57.03; H, 6.18; N, 16.63. Found: C, 56.75; H, 6.33; N, 16.57.

[Tris(3-(*N*,*N*-dimethylguanidino)phenyl)phosphine] trihydrochloride (17c): 94% yield; ^{1}H NMR (CD_3OD) δ 3.2 (s, 18 H), 4.8 (s, br, 9 H), 7.3−7.6 (m, 12 H); ^{31}P{^{1}H} NMR (CD_3OD) δ −0.5; ^{13}C{^{1}H} NMR (CD_3OD) δ 140.1 (J_{CP} = 13.2 Hz), 130.8 (J_{CP} = 21.2 Hz), 138.5 (J_{CP} = 8.1 Hz), 126.7, 131.6 (J_{CP} = 7.3 Hz), 133.4 (J_{CP} = 19.8 Hz), 157.5 (*C*N_3), 39.5 (N*Me*$_2$). Anal. Calcd for $C_{27}H_{39}Cl_3N_9P$: C, 51.72; H, 6.27; N, 20.10. Found: C, 51.48; H, 6.57; N, 19.83.

Synthesis of 17d by Metathesis Reaction. To 0.93 g (2.4 mmol) of **17a** dissolved in water (5 mL) was added an aqueous solution of 0.39 g (2.4 mmol) of NH_4PF_6 at ambient temperature. The precipitate formed was separated by filtration and dried in vacuo (25 °C, 0.1 mbar). After recrystallization from ethanol, **17d** was obtained as colorless crystals.

[Diphenyl((3-*N*,*N*-dimethylguanidino)phenyl)] hexafluorophosphate (17d): 81% yield; ^{31}P{^{1}H} NMR (CD_3OD) δ −1.4 (s, 1 P); −140.7 (septet, $^1J_{PF}$ = 710 Hz); ^{13}C{^{1}H} NMR (CD_3OD) δ 140.2 (J_{CP} = 14.2 Hz), 129.0 (J_{PF} = 16.3 Hz), 136.7 (J_{CP} = 5.1 Hz), 124.8, 131.9 (J_{CP} = 10.2 Hz), 131.7 (J_{CP} = 20.3 Hz), 136.5 (J_{CP} = 11.2 Hz), 133.6 (J_{CP} = 19.3 Hz), 128.5 (J_{CP} = 7.1 Hz), 129.0, 156.1 (*C*N_3), 37.8 (N*Me*$_2$). Anal. Calcd for $C_{21}H_{23}F_6N_3P_2$: C, 51.12; H, 4.70; N, 8.52. Found: C, 51.46; H, 4.73; N, 8.30.

General Procedure for Preparing the Catalyst Stock Solutions. Palladium acetate (100 μmol) and the phosphine ligands (500 μmol) were dissolved under nitrogen in 10 mL of degassed water followed by stirring at rt for 1−3 h. The resulting homogeneous solutions were stored under nitrogen at 4 °C in the refrigerator. The catalytic activity remained constant over months as evidenced by a standard C−C cross coupling between *p*-iodobenzoic acid and propiolic acid.

General Procedure for C−C Coupling Reactions. *p*-Iodobenzoic acid (10 μmol) and the alkyne coupling partner (20 μmol) were dissolved in 1 mL of an aqueous solvent mixture (30−50% CH_3CN/DMF). The reaction vial was thermostated in an oil bath at 35 or 50 °C, respectively. Addition of base (20−50 μmol) gave a homogeneous solution. The starting point for kinetic measurements of the coupling reaction was marked by the addition of catalyst stock solution (5 mol % Pd) and CuI solution in CH_3CN (ratio Cu/Pd 2:1).

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Supporting Information Available: $^{13}C\{^1H\}$ NMR spectra of **4c**, **11**, **14**, **15**, and **16c** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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